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EXAMINER	
MYERS, CARLA J	
ART UNIT	**PAPER NUMBER**
1634	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/760,048	TSANG ET AL.	
	Examiner	Art Unit	
	Carla Myers	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *4/2/07, 5/3/07, 10/31/07*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *10,11 and 13-23* is/are pending in the application.

4a) Of the above claim(s) *11,13-17,20,21 and 23* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *10,18,19 and 22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10/31/07and 5/3/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. This action is in response to the amendment filed April 2, 2007. Applicant's arguments have been fully considered but are not persuasive to overcome all grounds of rejection. All rejections not reiterated herein are hereby withdrawn. This action is made final.

Election/Restrictions

2. In the response of September 5, 2006, Applicant's elected, with traverse, the invention of Group II and in particular the primer of SEQ ID NO: 7. Accordingly, claims 11, 13-17, 20, 21 and 23 are withdrawn from consideration because these claims recite the use of additional, non-elected primers and probes.

It is noted that in the reply of April 2, 2007, Applicants acknowledge that claims 11, 13-17, 20, 21 and 23 will be rejoined with the elected invention upon the allowance of the claims from which they depend. However, as set forth below, claims 10, 18, 19 and 22 are not currently allowable for the reasons set forth below.

3. Applicant is advised that should claim 10 be found allowable, claim 19 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

Claim Rejections - 35 USC § 112

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 22 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 22 is indefinite over the recitation of "the sequence required for the selected detection reaction" lacks proper antecedent basis because the claim does not previously refer to any particular sequence that is required and does not previously refer to any particular selected detection reaction. Accordingly, it is unclear as to what constitutes the sequence that is required for a selected detection reaction.

Response to Remarks:

In the response, Applicants state that the rejection has been obviated by the amendments to the claims. However, the amendments to the claims do not address the indefiniteness of claim 22 as the phrase "the sequence required for the selected detection reaction" does not lack proper antecedent basis. The claim remains unclear as to what is intended to encompass the required sequence and what is intended to be encompassed by the selected detected reaction.

Claim Rejections - 35 USC § 103

5.The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 10, 18, 19, and 22 are rejected under 35 U.S.C. 103(a) as being unpatentable Yoon (WO 03/014397) in view of Nycz (Analytical Biochemistry. 1998. 259: 226-234)).

Yoon (page 7, line 24 through page 8, line 17) teaches methods for detecting enterovirus nucleic acids wherein the methods comprise amplifying a target nucleic acid sequence using a first amplification primer to produce an amplified target nucleic acid and detecting the amplified target nucleic acid as indicative of the presence of an enterovirus nucleic acid. The reference (pages 10-11) teaches that the method is one for detecting all enteroviruses, including coxsackie viruses, polioviruses, echoviruses, and enteroviruses 68, 69, 70 and 71. The reference (pages 10-11) also teaches that each enterovirus shares a genotype specific region which consists of nucleotides 164 to 526 of the 5' UTR. In particular, Yoon (page 11, 22 and 23 and Table 3) exemplifies methods wherein amplification of enteroviruses is performed using an EV2 primer which consists of conserved sequences of the 5'UTR. The EV2 primer of Yoon contains a

nucleotide sequence that is identical to the EV2 target binding sequence present in instant SEQ ID NO: 7:

EV2 primer of Yoon: ATTGT**CACCATAAGCAGCC**A

sequence of SEQ ID NO: 7: CACCATAAGCAGCC

Yoon does not teach detecting enterovirus nucleic acids using a primer which consists essentially of the full length sequence of SEQ ID NO: 7.

However, present SEQ ID NO: 7 is an SDA (strand displacement amplification) primer, which includes 3 regions: a) a first 3' region that is complementary to an enterovirus target binding sequence; b) a BsoBI restriction enzyme site 5' of the target binding sequence and which consists of the sequence of CTCGGG; and c) a 5' sequence that is not complementary to the target sequence and which consists of the sequence of CGATTCCACTCCAGACTT.

Methods for detecting target RNA sequences using SDA primers, as well as SDA primers containing 3' target binding regions, restriction enzyme sites, and 5' non-target binding regions, were well known in the art at the time the invention was made, and are specifically taught by Nycz.

Nycz (page 226) teaches methods for detecting a target RNA sequence comprising amplifying a target sequence using a first amplification primer to produce an amplified target nucleic acid and detecting the amplified target nucleic acid as indicative of the presence of the target RNA sequence. In particular, the amplification primer consists of three regions: a) a first 3' region that is complementary to a target binding sequence; b) a restriction enzyme site 5' of the target binding sequence; and c) a 5'

sequence that is not complementary to the target sequence (see col. 2, lines 58-67 through col. 3, lines 1-18). Nycz (page 227) teaches that the method is applicable to the detection of any RNA target and specifically exemplifies methods which detect HIV target nucleic acids.

In the method of Nycz (page 227), the amplification primer contains a BsoBI restriction enzyme site consisting of nucleotides CTCGGG, and a 5' non-target binding sequence of CGATTCCGCTCCAGACTT. Thereby the 5' non-target binding sequence of Pearson differs from that present in SEQ ID NO: 7 by a single nucleotide:

5' non-target region of Pearson: CGATTCC**G**CTCCAGACTT

5' non-target region of SEQ ID NO: 7: CGATTCC**A**CTCCAGACTT

Nycz (page 226) also teaches that SDA is an isothermal amplification method that provides greater than 10^{10} -fold amplification in 15 minutes. The reference (page 226) characterizes the disclosed method of quantitative RT-SDA as being "ideally suited for viral quantification because of its simple workflow, fast time to result and freedom from sophisticated equipment."

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Yoon so as to have amplified the enterovirus nucleic acids using the RT-SDA method of Nycz in order to have achieved the advantages clearly set forth by Nycz of providing a highly sensitive, rapid, simple and time effective method for detecting enterovirus nucleic acids. Such a modification of the method of Yoon would have resulted in the requirement to modify the EV2 primer of Yoon so that the primer was suitable for the RT-SDA reaction. The

resulting primer would thereby have included the BsoBI restriction enzyme site 5' of the target binding sequence and would have further included a 5' non-target binding sequence. While the 5' non-target binding sequence of Nycz differs from that of SEQ ID NO: 7 at one internal nucleotide, modification of the sequence of the 5' non-target binding region of the primer of Nycz to obtain additional 5' non-coding sequences, including the 5' non-target binding sequence of SEQ ID NO: 7, would have been obvious to one of ordinary skill in the art at the time the invention was made. Optimization of the sequences of the 5' region to select sequences which did not hybridize with the target sequence and which would hybridize at a similar Tm and work most efficiently in combination with additional primers would have been well within the skill of the art at the time the invention was made since the parameters which effect primer annealing, particularly with respect to SDA methods, were well known in the art. Accordingly, in the absence of evidence to the contrary modification of the 5' non-target sequence of Nycz to obtain the 5' non-coding sequence 5-'GATTCCACTCCAGACTT-3' would have been obvious to one of ordinary skill in the art and well within the skill of the art.

Further, modification of the primer of Yoon so as to have generated additional primers for the detection of enterovirus, and particularly modification of the primer of Yoon so as to have omitted the 5' terminal 6 nucleotides, would have been obvious to one of ordinary skill in the art. Designing primers which are equivalents to those taught in the art is routine experimentation. The parameters and objectives involved in the selection of primers were well known in the art at the time the invention was made.

Moreover, software programs were readily available which aid in the identification of conserved and variable sequences and in the selection of optimum primer pairs. The prior art is replete with guidance and information necessary to permit the ordinary artisan to design additional primers for the amplification of enterovirus. Additionally, Yoon specifically teaches that nucleotides 164 to 526 of the 5'-UTR of enteroviruses are highly conserved and that additional primers of varied lengths could be obtained from this region (see pages 10-11). Thereby, the ordinary artisan would have had more than a reasonable expectation of success of obtaining additional primers for amplifying enterovirus sequences. Thus, for the reasons provided above, the use of primers of SEQ ID NO: 7 in an RT-SDA method for detecting enterovirus would have been obvious to one of ordinary skill in the art.

Additionally, it is noted that the claims recite the language "consisting essentially of." Since this phrase has not been clearly defined in the specification and because there is no art recognized definition for this phrase as it applies to nucleic acids, the phrase has been interpreted as meaning that additional nucleotides may be present at either the 3' end or 5' end of the primer. To the extent that the claims encompass primers consisting of the sequence of SEQ ID NO: 7, additional modification of the primer of Yoon so as to have omitted the 3' nucleotide would have also been obvious to one of ordinary skill in the art in view of the teachings of Yoon and in the prior art of the sequences of enterovirus nucleic acids and methods for generating additional primers for detecting enterovirus nucleic acids. Thereby, in the absence of evidence to the contrary, use of SDA primers consisting of SEQ ID NO: 7 in the method for detecting

enterovirus would have been obvious to one of ordinary skill in the art and well within the skill of the art.

Regarding claim 18, Yoon does not teach detecting the amplified target nucleic acids using a labeled probe. However, Nycz (figure 1 and page 228) teaches that in the RT-SDA method, the primers are unlabeled and the target sequence is detected using a labeled probe complementary to the amplified target sequence. Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Yoon so as to have contacted the amplified target nucleic acids with a labeled probe in order to have facilitated the detection of the hybridization complex formed between the amplified target nucleic acid and probe, thereby providing an effective means for detecting the enterovirus nucleic acids.

Regarding claim 22, the resulting SDA-primer as set forth above includes a restriction site for facilitating the detection of the amplified target sequence.

Response to Remarks:

In the response, Applicants traverse this rejection. Applicants state that one of the unexpected results of Applicants' invention is that the primers have minimal cross-reactivity with rhinovirus. Applicants state that primers in the prior art cross-react with various strains of rhinovirus and cite Kesler in view of this finding.

This argument has been fully considered but is not persuasive. First, it is noted that all data provided in the specification was obtained using combination of primers which consist of particular nucleotide sequences. For example, the results set forth in Example 5 showing that RT-SDA was negative for all but one rhinovirus strain were

obtained using a combination of primers that included a primer consisting of SEQ ID NO: 7. The combination of RT-SDA primers appear to further include the primers of SEQ ID NO: 3, 4, 5, 6, 8, 9, and 10, together with the probes of SEQ ID NO: 11 and 12 (see page 26). However, the specification has not established any unexpected results obtained with any primer comprising a sequence consisting essentially of SEQ ID NO: 7, used in combination with any other undefined primers. Thus, Applicants asserted unexpected results are not commensurate in scope with the claims. Further, the specification (page 31) and reply indicate that primers used in the prior art method of Kesler show some level of cross-reactivity with rhinovirus strains. The specification and reply have not, however, established any unexpected results obtained with the claimed invention as compared to the cited closest prior art of Yoon. As discussed above, Yoon (pages 10-11) teaches that each enterovirus shares a genotype specific region which consists of nucleotides 164 to 526 of the 5' UTR. To specifically detect enteroviruses, Yoon (page 11, 22 and 23 and Table 3) designed an EV2 primer which consists of conserved sequences of the 5'UTR. Accordingly, Yoon specifically identifies sequences that are unique to enteroviruses. Since the EV2 primer of Yoon consists of conserved enterovirus sequences, and differs from the target binding region of present SEQ ID NO: 7 only in that it includes 5 additional 5' nucleotides and 1 additional 3' nucleotide, in the absence of evidence to the contrary, the EV2 primer of Yoon would be expected to be functionally equivalent to the target binding region of SEQ ID NO: 7. It is also noted that the present claims recite the claim language that the amplification primer comprises a sequence consisting essentially of a target binding sequence of SEQ ID NO: 7. In

view of the "a sequence" and "a target binding sequence" language, the claims read on primers that comprise any fragment of SEQ ID NO: 7. Further, because of the "having" and "consisting essentially of" language, the fragment of SEQ ID NO: 7 may be flanked by nucleotides of any length and identity. Accordingly, the claims read on amplification primers that include a target binding region that consists of the same EV2 primer disclosed by Yoon.

The response states that there is no motivation or suggestion in the cited references to modify the non-target binding region to change one internal nucleotide. Applicants assert that they believe the examiner has taken "official notice" and require a statement on the record that the examiner is taking "official notice." Applicants arguments have been fully considered but are not persuasive. The rejection does not take "official notice" of any particular facts. The rejection is based on the obviousness of modifying primer sequences, and particularly, modifying non-target binding primer sequences. It appears to be Applicants opinion that the ordinary artisan would not modify a non-target binding region of a primer without a specific teaching in a reference to change one particular nucleotide in the non-target binding sequence. This argument is not persuasive. Nycz teaches how to make SDA primers and provides extensive guidance on how to select the non-target binding sequences. The non-target binding region comprises a sequence that is not complementary to the target binding region (col. 2 lines 58-67 through col. 3, lines 1-18). While the non-target binding region of Nycz differs from that of the claimed invention by one nucleotide, the ordinary artisan having extensive knowledge of how to design primers that are not complementary to a

known target sequence, and having knowledge of how to use computer programs to compare nucleotide sequences, would have had more than a reasonable expectation of success of generating additional primers to be used in SDA amplification reactions, including the primer comprising the non-target binding region of SEQ ID NO: 7. Optimization of the sequences of the 5' region to select sequences which did not hybridize with the target sequence and which would hybridize at a similar Tm and work most efficiently in combination with additional primers would have been well within the skill of the art at the time the invention was made since the parameters which effect primer annealing, particularly with respect to SDA methods, were well known in the art. Accordingly, it is maintained that modification of the 5' non-target sequence of Nycz to obtain the 5' non-coding sequence 5-'GATTCCACTCCAGACTT-3' would have been obvious to one of ordinary skill in the art and well within the skill of the art.

Applicants state that the MPEP indicates that the language "consisting essentially of" limits the scope of the claims to specified materials or steps that do not materially affect eh basic and novel characteristics of the claimed invention. It is asserted that because modification of a primer can alter its binding activity. The response also states that the present primers do not cross react with rhinovirus and cite page 31 of the specification. These arguments have been fully considered but are not persuasive. First it is noted that the specification at page 31 does not in fact teach that a primer consisting essentially of SEQ ID NO: 7 does not cross react with any rhinovirus. Rather, the specification teaches the results of an RT-SDA assay in which the combination of primers consisting of SEQ ID NO: 3-9, used with the probes of SEQ ID

NO: 11 and 12 did not detect/cross-react with 5 out of 6 rhinoviruses. Accordingly, Applicants' response does not accurately characterize the data set forth in the specification.

Regarding the phrase "consisting essentially of, "the MPEP (see section 2111.03 – Transitional phrases) indicates that:

> A 'consisting essentially of' claim occupies a middle ground between closed claims that are written in a consisting of' format and fully open claims that are drafted in a comprising' format." PPG Industries v. Guardian Industries, 156 F.3d 1351, 1354, 48 USPQ2d 1351, 1353-54 (Fed. Cir. 1998). See also Atlas Powder v. E.I. duPont de Nemours & Co., 750 F.2d 1569, 224 USPQ 409 (Fed. Cir. 1984); In re Janakirama-Rao, 317 F.2d 951, 137 USPQ 893 (CCPA 1963); Water Technologies Corp. vs. Calco, Ltd., 850 F.2d 660, 7 USPQ2d 1097 (Fed. Cir. 1988). For the purposes of searching for and applying prior art under 35 U.S.C. 102 and 103, absent a clear indication in the specification or claims of what the basic and novel characteristics actually are, "consisting essentially of" will be construed as equivalent to "comprising."

In the present situation, the specification does not provide a clear indication of what constitutes the basic and novel characteristics of the invention. While the specification teaches that the combination of primers when used in an RT-SDA assay do not cross-react with 5 out of 6 rhinoviruses, there is no clear statement in the specification to indicate that this constitutes the novel aspects of the invention as it relates to methods using the individual primer SEQ ID NO: 7. Applicants response appears to indicate that any modification of the primer of SEQ ID NO: 7 could modify its hybridization properties. Thereby, it appears that Applicants are indicating that with respect to the present invention, the language "consisting essentially of" is intended to mean "consisting of." If this is the case, then the record should be clarified to indicate this definition for the phrase "consisting essentially of" or the claims should be amended to recite "consisting of" in place of "consisting essentially of." If Applicant asserts, contrary to their arguments, that additional nucleotides may be added to target binding

region of SEQ ID NO: 7, the interpretation of "consisting essentially of" as equivalent to "comprising" is maintained. The specification does not teach which particular nucleotides may be added to the target binding region of SEQ ID NO: 7 without altering the basic and novel characteristics of this primer. Further, Applicants have not established that the addition of the 5 nucleotides to the 5' terminus and 1 nucleotide to the 3' terminus of the target binding portion of SEQ ID NO: 7 alters the basic and novel characteristics of this primer.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Carla Myers whose telephone number is (571) 272-0747. The examiner can normally be reached on Monday-Thursday from 6:30 AM-5:00 PM. A message may be left on the examiner's voice mail service. If attempts to reach

the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla, can be reached on (571)-272-0735.

The fax phone number for the organization where this application or proceeding is assigned is (571)-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at (866)-217-9197 (toll-free).

/Carla Myers/
Primary Examiner, Art Unit 1634